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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,587	05/16/2001	Yoshiki Sasai	766.44	1416

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,587	SASAI ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/28/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *3-11,21 and 28-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 12-20, 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/29/02* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-71 are pending. Claims 1-2 and 12-20 and 22-27 are under current examination. Claims 3-11, 21 and 28-71 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group(s), there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Election/Restrictions

Claims 3-11, 21 and 28-71 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group(s), there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Applicant's election without traverse of Group I [claims 1-2 and 12-27] in Paper No. 13 is acknowledged.

Applicants further elect the following species with respect to Group I:

1. Species A – a nervous system cell
2. Species C – an ectodermal cell
3. Species Q – bone morphogenetic protein 4
4. Species U – A treatment with an antitumor agent
5. Species i – mitomycin C
6. Species x – microwave fixation
7. Species hh – a fetal primary culture fibroblast

8. Species oo – an embryonic stem cell established by culturing an early embryo before implantation

The following species elected by Applicant are withdrawn from consideration as being drawn to non-elected groups.

1. Species E – A neural stem cell [claim 6 is generic]

2. Species I – A dopaminergic neuron [claim 8 is generic]

3. Species M – A cell of neural tube before determination of dorso-ventral axis [claim 10 is generic].

4. Species rr – Disorder of a nervous system cell [claim 68 is generic]

5. Species tt – Alzheimer disease [claims 67-69 are generic]

6. Species hhh – Burn [claims 67-69 are generic]

Note that claim 21, which depends on claim 19 is directed to a non-elected invention [treatment for tissue fixation]. Accordingly, claim 21 is withdrawn from consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 5/16/00 and 9/25/00. It is noted, however, that applicant has not filed a certified copy of the Japan 2000-144059 and Japan 2000-298019 applications as required by 35 U.S.C. 119(b).

Drawings

The drawings are objected for reasons advanced on the Notice of the Draftsperson's Patent Drawing Review [Form PTO 948]. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Applicant(s) is/are hereby notified that the required timing for correction of drawings has changed. See the last 6 lines on the sheet, which is attached, entitled "Attachment for PTO-948 (Rev. 03/01 or earlier)". Due to the above notification Applicant(s) is/are required to submit drawing corrections with the time period set for responding to this Office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 12-20 and 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of inducing the differentiation of embryonic stem cells by culturing in the presence of a stroma cell, which is recognized by a monoclonal antibody produced by a hybridoma FERM BP-7573. Claims 23-27 depend from claim 22 and are thus included in this rejection. The specification teaches that mouse spleen cells were used for the production of hybridomas [see p. 120 of the specification]. In particular, three types of anti-human PA6 antibodies, KM1306, KM1307 and KM1310 were obtained. The specification teaches that the KM1310 producing hybridoma cell, [FERM BP-7573] was deposited on April 27, 2001, in International Patent Organism Depositary [see pp. 120-121, bridging ¶]. Since the FERM BP-7573 hybridoma cell line is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the hybridoma cell line is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make" may be satisfied by a deposit of the cell line. The specification does not disclose a repeatable process to obtain the cell line and it is not apparent if it is readily available to the public. It is noted that Applicant has deposited the cell line to the International Patent Organism Depository in Japan, but there is no indication in the specification as to public availability. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by

Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell line has been deposited under the Budapest Treaty and that the cell line will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807);

and,

(e) the deposit will be replaced if it should ever become inviable.

Once the deposit of the FERM BP-7573 hybridoma has been resolved, the claims will be subject to the following scope of enablement: methods for inducing differentiation of pluripotent embryonic stem cells into ectodermal cells, the specification does not reasonably provide enablement for methods of inducing differentiation of embryonic stem cells for the breadth claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to methods for inducing differentiation of an embryonic stem cell into an ectodermal cell, which comprises culturing the embryonic stem cell under non-aggregation conditions.

The claims encompass both pluripotent and totipotent human ES cells. However, the specification is not enabling for the breadth of the claims. In particular, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, p. 214, S*ummary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

"The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of <u>any</u> species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (**Journal of Clinical Investigation**, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 1558, column 2, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal, the state of the art supports that only <u>mouse ES cells</u> were available for use for production of transgenic mice.

This is further supported by Pera *et al.* [**Journal of Cell Science** 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "Thus far, <u>only</u> mouse EG or ES cells meet these generic

criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." [See p. 6, 2nd column, last paragraph].

Accordingly, in view of the unpredictable and undeveloped state of the ES cell art and unavailability of any totipotent ES cells, for the breadth claimed, and lack of guidance or teachings provided by the specification for totipotent ES cells isolated from any species for the breadth claimed, it would have required undue experimentation for one skilled in the art to use the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 12-20 and 22-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, as written is indefinite. The claim recites that the ectodermal cell is "capable of" differentiating into a nervous system cell. It is unclear whether this characteristic actually occurs or that the cell could potentially do these described things. "Capable of" implies a latent property and the conditions for the latent

property must be clearly defined. Therefore, it is unclear if the latent property is ever obtained. Claims 12-20 and 22-27 depend from claim 2.

Claims 12-20 and 22-27 refer to claims which have been withdrawn from examination, which renders the claims confusing. For example, claim 12 recites, "The method according to any one of claims 1 to 11" in line 1 of the claim. However, only claims 1 and 2 are under current examination. Appropriate correction is requested.

Claim 21, as written, is unclear. The claim recites that the monoclonal antibody is produced by a hybridoma FERM BP-7573. This recitation implies that there is more than one such hybridoma. It is suggested that the claim be written to state the hybridoma. Claims 23-27 depend from claim 21.

Claim 27, as written, is vague. The claim recites that the method "does not substantially accompany" in line 2 of the claim. This is unclear because the metes and bounds of the term "substantially" cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 14, 24, 26 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by van Inzen [**Biochim et Biophys Acta** (1996) 1312:21-26].

The claims are directed to methods for inducing differentiation of an embryonic stem cell into an ectodermal cell, which comprises culturing the embryonic stem cell under non-aggregation conditions, and in further embodiments, the ectodermal cell is capable of differentiating into a nervous system cell and the non-aggregation conditions do not mediate an embryoid body, the embryonic stem cell is established by culturing an early embryo before implantation, and the embryonic stem cell is differentiated into an ectodermal cell at an efficiency of 5% or more.

van Inzen teach neuronal differentiation of mouse ES cells by retinoic acid. In particular, undifferentiated ES-E14 cells [derived from mouse blastocysts], ES-D5 [isolated from the inner cell mass of non-delayed blastocysts] and ES-D3 cells [derived from 129/Sv+/+ blastocysts] which were split and induced to differentiate in a monolayers in the presence of retinoic acid [see p. 22, col. 1, *Materials and Methods*, 2.1, Cell Culture]. Van Inzen teach that the differentiated cells were then analyzed and it was found that after 3 days of retinoic acid treatment, up to 50% of the cell population stained positive with the neuronal specific antibody, GAP-43. On the day 5 post-differentiation induction, a significant portion (~50%) of the glial-like cells stained positive for NF-165 antibody [an intermediate filament specific for neurons]. See p. 24, 1st column.

Accordingly, van Inzen anticipate the claimed invention.

Claims 1, 2, 12-15, 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalyani *et al.* [**The Journal of Neuroscience** (1998) 18:7856-7868].

The claimed invention is directed to methods for inducing differentiation of an embryonic stem cell into an ectodermal cell, wherein the ectodermal cell is capable of differentiating into a nervous system cell. In further embodiments, the culturing is carried out in the presence of BMP-4, sonic hedgehog, and under non-aggregating, serum-free culturing conditions. In further embodiments, the culturing is carried out in the absence of retinoic acid, the embryonic stem cell is differentiated into an ectodermal cell, or an ectoderm-derived cell, and does not substantially accompany differentiation induction of a mesodermal system cell.

Kalyani teach neuronal restricted precursors [NRPs] which were isolated from rat embryos [see p. 7857, 1st column, *Materials & Methods*]. They teach that E-CAM+ cells were purified from dissociated cells using a specific antibody-capture assay and the dissociated cells were plated onto an NCAM antibody-coated dish. Bound cells were then mechanically scraped off and plated on fibronectin-laminin coated dishes in 1 ml of NEP medium. Theses NRP cells were then induced to differentiate into multiple neuronal phenotypes by planting on poly-lysine/laminin coated dishes, and in some experiments, neuronal differentiation was induced by the addition BMP-2 or BMP-2 [see p. 7857, col. 2, last ¶]. The effect of sonic

hedgehog [Shh] and BMP on the NRP cell differentiation was assessed by supplementing the NEP medium with Shh, BMP-2 or BMP-4. Kalyani teach that neuronal precursors such as NRPs can develop into mature neurons of multiple phenotypes, and that either application of retinoic acid or FGF can promote differentiation. Further, it was note that BMP-2 and BMP-4 was added to the cultures, a dramatic reduction of cell division was noted [see p. 7863 and Figure 6K] and that addition of Shh appeared to be mitogenic [see p. 7863, 3rd ¶ and Figure 6J].

Accordingly, Kalyani teach the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Deborah Crouch

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